The advanced-DiaRem score improves prediction of diabetes remission One year post-Roux-en-Y gastric bypass

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Short running title: Prediction of diabetes remission after Roux-en-Y gastric bypass

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Abstract (250 words)

Aims/hypothesis: Some, but not all type 2 diabetic patients, experience Diabetes remission (DR) post- bariatric surgery (BS). It, thus, is critical to develop predictive scores applicable in clinical routine. The DiaRem score is a relevant predictive score for post-Roux-en-Y gastric bypass (RYGB) DR, but might not be accurate for all patients across the entire spectrum of score categories. We aimed to develop an optimized DR predictive score (the Advanced-DiaRem).

Research Design and Methods: We used a retrospective French cohort (N=1866) with 352 type 2 diabetes patients followed one year post-RYGB. We developed the Advanced-DiaRem in a test cohort (N=213) and examined its accuracy in independent cohorts from France (N=134) and Israel (N=99).

Results: Adding two clinical parameters (diabetes duration and glucose-lowering agent number) to the original DiaRem and modifying the score penalization led to an improved Ad-DiaRem predictive performance. The Ad-DiaRem score displayed an improved Area under the ROC and predictive accuracy as compared to the DiaRem score (respectively 0.911 vs. 0.856 and Acc=0.841 vs. 0.789;p=0.03), thus correcting classification for 8% patients initially misclassified with the DiaRem. Using the Advanced-DiaRem, there was also less misclassification in the middle scoring zone. This improved prediction was confirmed in independent cohorts.

Conclusion We propose the Ad-DiaRem score, which includes two additional clinical parameters, as an optimized score with improved accuracy to predict DR one-year post-RYGB. Owing to the gain in patient classification, this score might be helpful for personalized management of diabetic subjects when considering BS in routine care, ultimately contributing to precision medicine.

Keywords. type 2 diabetes mellitus, bariatric surgery, obese, diabetes remission.

Abbreviations.

Ad-DiaRem: Advanced DiaRem

BS: bariatric surgery

DPP-IV: dipeptidyl peptidase-4 inhibitors

DR: diabetes remission (including complete remission and partial remission)

FN: false negative rate

FP: false positive

GLP-1 : glucagon-like peptide-1

PDR : partial diabetes remission

RYGB : Roux-en-Y gastric bypass

scAT : subcutaneous adipose tissue

TZD: thiazolidinedione

Introduction

Bariatric surgery (BS) elicits beneficial effects of major and sustained weight loss with improved metabolic comorbidities. BS indeed improves glycaemic control and even induces diabetes remission (DR), which can be complete or partial (PDR), defined by fasting glycaemia and HbA_{1c} normalization without glucose-lowering treatment one year post-BS [1]. These observations recently led to revised guidelines, which recommend BS in the treatment algorithm of type 2 diabetes patients, at any stage of obesity [2]. These guidelines are expected to substantially augment the already increasing number of BS interventions worldwide [3]. However, despite beneficial effects of BS on patients' metabolic conditions, there is significant inter-individual variability for patients experiencing type 2 diabetes improvement. This outcome is dependent on various parameters, including BS procedure type and type 2 diabetes severity before surgery.

A meta-analysis using an earlier DR definition found that 78% of type 2 diabetes patients achieved DR post-BS [4]. However, when applying the latest ADA proposed definitions [1] considering all BS procedures, the proportion of patients experiencing DR decreased to 35%. When specifically focusing on Roux-en-Y gastric bypass (RYGB), 1 year DR occurs in 40-60% of patients [5, 6]. This remission rate decreases to 37% 5 years post-RYGB, denoting an important prevalence of relapse [7]. Furthermore, although BS patients display overall beneficial health outcomes, perioperative morbidity and mortality rates remain at 3.4% and 0.3%, respectively [4]. Deleterious effects, such as nutritional deficiency, are also observed in the different BS types [8, 9]. [8]Together, the anticipated increasing number of BS procedures and uncertainty in predicting patients' clinical outcomes, both short- and long-term, emphasizes the need to establish useful and clinically applicable tools to predict metabolic/bariatric surgery

outcomes [2].

Current clinical predictors include preoperative clinical variables (i.e. young age, short diabetes duration, type 2 diabetes control [e.g. low HbA_{1c}], no insulin requirement), as well as post-BS outcomes (e.g. significant post-BS weight loss). Several scoring systems or statistical models based on these and other variables [10–13] currently help predicting DR post-BS. Among them, the DiaRem, a scoring system based on preoperative age, HbA_{1c}, and the use of some glucose-lowering treatments, has a predictive accuracy of 84% one year post-RYGB [14]. However, the use of the DiaRem score across the scoring spectrum has limitations. BS patients with a medium DiaRem score (i.e. score between 8-17) only display a 50% probability of DR [13]. Also, one-third of subjects with a high score—those predicted to have diabetes non-remission—also attain DR [15]. Importantly, the current DiaRem does not take into account novel glucose-lowering agents such as GLP-1 analogs, DPP-IV inhibitors, or SGLT2 inhibitors, which may also influence DR [13]. Collectively, these observations prompted us to examine the ability to optimize this current scoring system and provide gain in patient classification before BS.

We aimed at developing an improved predictive score (e.g. the advanced (Ad)-DiaRem) for DR post-BS by adding easy-accessible clinical variables, and tested its predictive accuracy in a test cohort. We then examined the relevance of this improved score in two independent confirmation cohorts from France and Israel.

Research Design and Methods

Study design and participants

We leveraged our ongoing patient cohort (“BARICAN” recorded in CNIL n°1222666),

followed in the Pitié-Salpêtrière hospital Nutrition department (Paris, France), which consists of obese patients meeting standard guidelines for BS [16]. We only selected patients who underwent RYGB, excluding revisional surgery, and with a very detailed clinical data set at one year follow-up. Intending to build this putative optimized score, we identified type 2 diabetes patients with baseline (T0) bio-clinical and anthropometric variables, obesity-related disease information and detailed treatment usage, blood metabolic and inflammatory parameters, adipocyte size, and liver histological diagnosis

The first cohort (i.e. “test cohort”), which consisted of 213 type 2 diabetes subjects with complete data for all of the above cited-parameters, enabled the development of two different scores: an Advanced-DiaRem (Ad-DiaRem), including simple clinical parameters (that significantly differed at baseline between DR and non-DR patients) to the existing DiaRem, and (ii) a Costly-DiaRem, constructed for patients falling in the Ad-DiaRem middle zone in order to further improve prediction accuracy.

A French confirmation cohort also coming from the “BARICAN” cohort consisted of 134 type 2 diabetes patients with variables used in the Ad-DiaRem (Table 2). We further examined the Ad-DiaRem in another independent cohort from Israel, comprising 99 type 2 diabetes patients who only had RYGB as described previously [17]. These patients were included in the retrospective electronic medical records of Clalit Health Services (CHS) and included type 2 diabetes patients who underwent BS from 1999 to 2011, with follow-up data accessed until December 2014. Data from the CHS electronic database included the parameters from the DiaRem and Ad-DiaRem (see Figure 1 for study flow chart).

Ethical approval was obtained from the French Research Ethics Committee of CPP Ile de

France-1 N°13533 and the Rabin Medical Center Ethics Committee approved the Israeli retrospective electronic medical records study. All patients signed an informed consent form.

Definition of diabetes and one-year remission outcomes

type 2 diabetes was defined according to ADA criteria [18]. In the French and Israeli cohorts, one-year remission outcomes were defined according to the latest ADA definition [1] described in Table 1. We considered complete (DR) and partial (PDR) remission subjects as the remission group (DR+PDR), because they displayed blood glucose control normalization without glucose-lowering agents.

Test cohort's bio-clinical, anthropological and histological parameters

Baseline clinical information on diabetes duration (i.e. duration up to RYGB intervention), glucose-lowering agents, and obesity-related comorbidities and treatments (e.g. hypertension, obstructive sleep apnea and dyslipidemia) were collected as described [16]. Glucose-lowering medication groups were classified as follows: glucagon-like peptide-1 (GLP-1) analogs, dipeptidyl peptidase-4 inhibitors (DPP-IV), sulfonylureas, thiazolidinedione (TZD), glinides, α-glucosidase inhibitor, metformin, and insulin (basal and/or bolus). The number of glucose-lowering agents prescribed was considered the sum of the above drug categories.

Blood samples were collected after a 12-hour overnight fast at baseline. Pancreatic beta-cell function (insulin secretion) and insulin resistance were estimated using HOMA-β and HOMA-IR, respectively [19]. Body composition was evaluated by whole-body, dual-energy X-ray absorptiometry scan (DXA, Hologic Discovery W) [20].

Adipocyte diameter, which enabled the calculation of adipocyte morphology [21], was

evaluated with Perfect Image (Clara Vision, Verrières le Busson, France) from subcutaneous adipose tissue (scAT) needle-aspirated biopsies after collagenase digestion as described [22]. Perioperative surgical liver biopsies were collected to assess NAFLD or NASH using the SAF score [23, 24].

The DiaRem Score

The DiaRem, initially established to predict post-BS DR+PDR probability, was calculated for each patient using age, HbA_{1c}, some glucose-lowering medications, and insulin use, with a defined weight as described in [13] ranging from 0 to 22 (Suppl. Table 1).

Development of an optimized scoring system – Advanced DiaRem (Ad-DiaRem) Score

We examined 43 baseline variables (11 clinical parameters, 27 laboratory variables and 5 scWAT and liver biopsy parameters (**Table 1**)) as potential variables that could improve the DiaRem predictive power. Multivariate logistic regression was performed to estimate the Odds Ratio (OR) of potential DR+PDR predictors. The parameters whose OR were significant (i.e. $p<0.05$) were selected and included into the Ad-DiaRem scoring system, (i.e. all the parameters included in the DiaRem, plus two easily-accessible clinical parameters, (i.e. the number of glucose-lowering agents and diabetes duration).

Statistical analyses

Categorical variables are expressed as numbers and percentages, continuous data as mean±SD. Categorical data were analyzed using Fisher's exact test for two groups. Continuous data were analyzed using the Student's t-test. The analyses were adjusted by age. Two-tailed P values were

considered significant at $P<0.05$. All analyses were conducted using R software version 3.0.3 (http://www.r-project.org) and GraphPad Prism 6.0.

Learning Ad-DiaRem: A clinical scoring system should be able to select relevant clinical variables, propose interpretable clinical thresholds, and estimate weights for corresponding bins. We applied a machine learning method that simultaneously learns the restricted set of informative variables to retain. This method which associates interpretable binning to map with each class variable (DR+PDR or NDR), and provides optimal weights to associate with these bins contributing to the score. For machine learning, we minimized *empirical risk* given the diabetes cohort, and performed 10-fold cross validation to avoid possible overfitting. Specifically, as a classification algorithm, we used a sparse support vector machine. To optimize the problem of the score learning, we formulated it as a linear integer programming task, and we used the IBM ILOG CPLEX Optimization Studio (http://www-03.ibm.com/software), which is a state-of-the-art solver for constrained optimization problems. We added integrity constraints to our task, so that the resulting weights are integers. Also, constraints shrink similar variables to each other, creating bins, and ordering them. The computations were done with R version 3.1.3, and "Rcplex" package which is the interface to the IBM CPlEX Studio. The predictive performance of different scores was evaluated by the area under the Receiver Operating Characteristic (AUROC) curve using DeLong method.

Data availability: All data used for analyses in the current paper are available on request from the authors.

Results

Clinical variables associated with one-year diabetes remission post RYGB

In the test cohort, 64% subjects achieved one-year remission (DR+PDR) (Fig 1), concordant with previous reports [25]. Compared to NDR patients, DR+PDR patients were younger, had significantly lower FPG and HbA_{1c}, and were less likely to be treated by insulin or by oral glucose-lowering agents other than metformin pre-surgery (Table 1, Fig 2a). DR+PDR patients displayed a significantly higher BMI, higher DXA-evaluated fat mass and less abdominal fat distribution. Importantly, after adjustment for age, although differences in fat mass and its deleterious deposition (android/gynoid fat mass) remained significant, BMI did not. DR+PDR patients also exhibited a shorter type 2 diabetes duration, and potentially increased beta-cell function as estimated by HOMA-β (Table 1). These differences remained significant after adjustment for age. The gender ratio was not significantly different between groups.

Although adipocyte diameter was increased in type 2 diabetes patients compared to non-diabetic patients (data not shown), it was not significantly different between groups when examining the one-year outcome (i.e. DR+PDR vs. NDR). Liver fibrosis scores (upon liver biopsies) were more severe in NDR patients as compared to DR+PDR patients (Suppl. Figure 1), whereas other liver alterations (i.e. steatosis, inflammation activity, NAFLD/NASH scores) were similar between groups. This exploration revealed that (i) DiaRem variables differed between DR+PDR and NDR groups, and (ii) additional factors (number of glucose-lowering agents, diabetes duration and body composition parameters) also varied.

DiaRem score in the test cohort

When evaluating the DiaRem in our test cohort (Suppl Table 1), we found an AUROC of 85% (Fig 2b). Using the Youden method, the threshold to diagnose remission was calculated to be 7 (i.e. subjects with a DiaRem <7 should remit diabetes), confirming our previous findings in

another independent group [14]. Although the overall predictive accuracy of DiaRem was 78.9% (Fig 2b), the false positive rate (FP, remission was predicted despite NDR, n=9) and false negative rate (FN: non remission was predicted despite their exhibiting remission n=41) were quite high. Positive predictive value was high (PPV=0.91) but negative predictive value was much lower (NPV=0.62).

Subsequently, patients were stratified into five groups according to their DiaRem score: 0-2 (highest probability of DR+PDR), 3-7, 8-12, 13-17, 18-22 (lowest probability of DR+PDR) (Fig 2c). A high proportion of subjects with low scores (0-2 and 3-7 groups) achieved remission, indicating a good predictive value of DiaRem for subjects in this range (Fig 2c). However, about half of the subjects with scores ranging from 8-12 attained DR+PDR, demonstrating a poor predictive performance in this intermediate zone. We highlighted a high degree of misclassification in this middle zone (i.e. 27 patients (12.6%) with a DiaRem score between 8 and 17 still experienced remission) (Fig 2c). Together, the majority of the DR+PDR and NDR groups were not readily separable by DiaRem, with an overlap between the score ranges that cumulatively included 80% of either group (Fig 2d).

These results indicate a satisfactory predictive value of the DiaRem score for the extreme ranges, but a lot of patients remained incorrectly classified. This prompted us to evaluate the relevance of other variables in predictive accuracy.

Advanced DiaRem score improves prediction of Diabetes remission one-year post-RYGB

We examined baseline parameters that significantly differed between DR+PDR and NDR patients (i.e. $p<0.05$, Table 1) to develop an improved predictive score (Ad-DiaRem; Suppl Table 2). After adjustment for the 4 parameters already present in the DiaRem, the OR (Odds Ratio of glucose-lowering agents number, diabetes duration, DXA-evaluated body composition

but not BMI) were significant. Since DXA might not be easily accessible in all clinical settings, we first tested whether including only two additional clinical parameters would be sufficient to improve the DiaRem accuracy.

The Ad-DiaRem (Table 2) led to a better classification of DR+PDR patients with an improved AUROC and accuracy as compared to the DiaRem (respectively 0.911 vs. 0.856 and Acc=0.841 vs.0.789; p=0.03) (fig 2b,e). Compared to the DiaRem (Fig 2d), the Ad-DiaRem created a better separation of 80% of patients that achieved DR+PDR versus patients that did not (i.e. the majority (80%) of both groups (DR+PDR and NDR) did not overlap with the Ad-DiaRem (Fig 2e). Additionally, the Ad-DiaRem demonstrated better positive and negative predictive values (0.93 and 0.72, respectively) compared to the DiaRem (VPP=0.91 and VPN=0.62), thus leading to improved classification of 16 patients (8% more) who were initially misclassified. In total, the DiaRem correctly classified 164/213 patients from the test cohort whereas 180/213 patients were correctly classified by the Ad-DiaRem.

The predictive improvement was most noticeable for patients with low scores (0-2 and 3-5 groups; i.e. DR+PDR patients) or high scores (15-21, remaining type 2 diabetes). As a consequence, the AUROC and accuracy calculation of Ad-DiaRem was better in extreme ranges as compared to the DiaRem score, nearly reaching significance (Fig 2f, 2g, p=0.06 for comparison between scores 0-5 and 17-21 in the DiaRem and Ad-DiaRem).

For patients in the middle scoring, the Ad-DiaRem correctly reclassified 12 of 24 patients the DiaRem incorrectly predicted as NDR. Although AUROC and accuracy were increased in this middle zone for Ad-DiaRem (Fig 2h), the difference did not reach statistical significance comparing the two scores.

We next examined the Ad-DiaRem prediction accuracy in French and Israeli confirmation

cohorts. In the French cohort, 57% of the subjects achieved one-year remission one year post-BS (Fig 1). Fig 2b, 2i shows that, compared to the DiaRem, the Ad-DiaRem better classified patients in the French cohort, with an increased proportion of subjects with low score (0-2 and 3-5 groups) achieving remission, and a very high proportion of patients with high scores (17-21) remaining type 2 diabetes. This improvement remained in the different scoring sub-categories (Fig 2f, 2g, 2h). As compared to the DiaRem, the Ad-DiaRem score correctly reclassified 10 patients (7.4%), and the overall accuracy and AUROC of Ad-DiaRem in predicting DR+PDR patients (vs. NDR) was superior in the test and confirmation cohorts (Fig 2b, p=0.03). NPV also increased with Ad-DiaRem in this confirmation cohort as compared to the DiaRem (0.82 vs. 0.75, respectively). A similar added value of the Ad-DiaRem was found when comparing patients with complete DR vs. NDR in the test and confirmation cohorts (i.e. excluding patients with PDR (Suppl Fig 2).

In the Israeli group from HMO Clalit, comprising 99 type 2 diabetes patients, 57% displayed DR+PDR. Similar to the observations made in French cohorts (Suppl Table 4), Ad-DiaRem clearly separated the majority (80%) of the DR+PDR group from the NDR (Fig 2j, 2k), whereas DiaRem exhibited an overlap between the groups. Consistently, the AUROC increased from 0.825 with DiaRem to 0.882 with Ad-DiaRem (Figure 2l).

Added value of other bioclinical variables to predict diabetes remission post-RYGB?

To evaluate if we could further improve Ad-DiaRem performance for patients with scores in the middle zone (8-14), we tested the interest of adding other variables such as DXA-measured fat mass, fat-free mass proportion, fat mass/fat-free mass ratio, serum CRP and HOMA-β. These variables significantly differed between DR+PDR and DNR patients at baseline.

Using a binning method, we developed a Costly-Diarem scoring system, which penalized for low fat mass (%), high fat-mass/fat-free mass ratio, high android/gynoid fat mass ratio, high serum CRP and low HOMA-B (see Suppl Table 5). Despite the inclusion of these additional bioclinical variables providing deeper phenotyping, the Costly-DiaRem did not perform better than the Ad-DiaRem in any scoring range (Supp Fig 3). When adding only HOMA-β on top of the Ad-DiaRem, prediction was not improved either (data not shown).

Discussion

Here, we show that the Ad-DiaRem score improves one year post-RYGB predictive accuracy of Diabetes remission (DR+PDR) as compared to the currently proposed DiaRem score in a population of severely obese type 2 diabetes individuals. From 347 French type 2 diabetes patients (214 with DR+PDR), 26 patients were correctly reclassified using the Ad-DiaRem. This improved score adds easily-recorded clinical data (i.e. diabetes duration and glucose-lowering agents' number) and modifies the scoring penalization of variables. Ad-DiaRem significantly increases the predictive performance of DR+PDR as well, evidenced in French and Israeli cohorts. Developing an accurate scoring system to better stratify BS patients is becoming necessary regarding the number of BS procedures increasing worldwide [3]. This is compounded by new guidelines for type 2 diabetes management now recommending BS in the treatment algorithm of type 2 diabetes patients with a lower BMI cutoff [2]. Not all patients display the same beneficial outcomes, both in the extent of weight loss [26] and metabolic improvements [4]. Therefore, the development of reliable predictive tools will help routine care decision making and, in the future, to innovate personalizing patient's pre- and postoperative care pathways.

The DiaRem score, recently created using Cox regression analysis with 5-year follow-up

data in 690 subjects [13], demonstrated good predictive performance for one-year remission, despite slightly lower accuracy in confirmation cohorts [13]. Here, we confirmed the performance of the DiaRem score in the French and Israeli cohorts but a significant number of patients remained misclassified [13, 15], primarily in the medium score range (8-17), which comprised about one-third of cohorts. The Ad-DiaRem significantly decreased the predictive errors for the overall cohorts and subjects within the medium DiaRem scoring range. The Ad-DiaRem score exhibited a PPV of 0.93 and NPV of 0.72 in predicting DR+PDR in the test cohort, thus improving the predictive accuracy of the previously-published DiaRem.

The improved performance of Ad-Diarem was likely due to multiple factors. First, the DiaRem score included patient age, a rather indirect marker of diabetes duration. Although with increasing age patients might have a longer diabetes duration, it is known that with the dramatic increase in obesity prevalence worldwide, type 2 diabetes now occurs earlier [27]. Therefore, the small penalty assigned for age below 40 in the DiaRem score might not be fully accurate for everyone [13]. Diabetes duration is regarded as a consistent marker of disease progression, and recognized as the best predictor of post-BS diabetes remission [2, 28, 29]. Because this parameter was not available in the Still et al. database used for the DiaRem calculation, it could not be integrated [13]. Diabetes duration was integrated in ABCD, another predictive tool for DR+PDR post-BS [12]; however, this method did not perform as well as the DiaRem [14]. The ABCD scoring system might not be convenient for routine use as it relies on fasting C-peptide, an expensive serum marker not easily available in routine care. Admittedly, diabetes duration is not absolutely accurate. It is usually self-reported and the true onset of disease is indolent. Frequently, type 2 diabetes is diagnosed long after beta-cell function has declined [30]. Still, diabetes duration is easy to collect, and its value demonstrable in the Ad-DiaRem. Secondly, the

DiaRem does not take into account currently available drugs for type 2 diabetes treatment, mainly DPP-IV inhibitors and GLP-1 analogs. This latter class is widely used in obese type 2 diabetes patients, because it improves glucose control and decreases weight in some patients [31]. We reasoned that taking into account the overall number of drugs might be more reflective of disease progression during the preoperative stage. Thus, we integrated this information into the Ad-DiaRem (Suppl Table 1). Furthermore, since association of glucose-lowering agents are not standardized among countries [32, 33] and are given according to patient's tolerance and secondary effects, we believe that adding the number of glucose-lowering agents in our score will better take into account patient's individual heterogeneity.

By using this retrospective cohort of type 2 diabetes patients undergoing RYGB that were extensively phenotyped at baseline, we also describe new clinical parameters associated with NDR. Compared to DR+PDR patients, NDR patients had less adipose tissue (lower fat mass); however, NDR patients displayed increased android-fat mass repartition at baseline, which is recognized as a detrimental for metabolic complications [34]. Patients with NDR also displayed liver fibrosis more frequently.

The Ad-DiaRem improved the predictive accuracy compared to the DiaRem, but did not fully solve patient misclassification in the score middle zone. Despite our effort to add other detailed phenotypic characteristics differing at baseline between DR+PDR and NDR (i.e. body composition data and insulin secretion index) to the Ad-DiaRem, we were unable to further improve prediction accuracy. This opens the interest in testing other biological markers. For example, recent literature points to the importance of genomic variation (SNPs) related to insulin secretion in the prediction of diabetes remission post-BS, suggesting that measures related to pancreas failure to (hyper-)secrete insulin might be of interest. The added value of genetic

scoring must be examined in comparison with scores using clinical variables and other variables measurements linked to patients' impaired metabolism. However, it is unknown whether adding more complex patient information derived from high throughput analysis such as systemic proteomics, metabolomics, or metagenomics [35, 36] or tissue alterations would be helpful in improving prediction, particularly in patients in the middle range of the score. As such, we previously described that adipose tissue fibrosis associates with reduced weight-loss post-BS [22, 37]. Whether adipose tissue scoring might be useful to predict post-BS outcomes is an unanswered question.

Our study has some limitations. First, we focused on DR+PDR one-year post-RYGB. Studies now demonstrate that remission is not long-lasting in all patients [28]. For instance, 43% of subjects who achieved one-year DR+PDR later displayed type 2 diabetes recurrence five years post-BS [38]. This highlights the need to evaluate long-term glycaemic outcomes in type 2 diabetes and test the relevance of the Ad-DiaRem in the long term [39]. Indeed, type 2 diabetes is a progressive disease that worsens with time [40, 41] and BS may only induce transient remission followed by resurgence or exacerbation. Despite this, while not all patients undergo remission, they still improve their glycaemic control as seen with a reduction of the number of glucose-lowering agents and HbA_{1c} as observed in two long term randomized control trials [7, 42]. When tested for prolonged remission 5 years post-RYGB, DiaRem was not optimal for predicting remission in patients with high scores [39]. Another perspective is to test the Ad-DiaRem in other BS procedures, in particular post-sleeve gastrectomy, a procedure increasing worldwide [3]. Finally it should be noted that we tested the validity of our Ad-DiaRem solely in a population of severely obese individuals, which, to date, represents the majority of BS candidates [43, 44]. However, the Ad-DiaRem should be further tested in diabetic

patients with less severe obesity as these patients will increasingly become candidate for BS procedure based on recent ADA recommendations [45].

Conclusion: We described the benefits of the Ad-DiaRem, highlighted by its ability to improve Diabetes remission prediction while improving the separation between patients predicted to have DR+PDR and NDR. In the future, patients predicted to have type 2 diabetes non-remission might be proposed a patient care pathway with more intensive follow-up and/or increased physical activity advices. These approaches have to be further tested and new guidelines proposed.

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Author contributions All authors provided: (1) substantial contributions to conception and design, acquisition of data, or analysis and interpretation of data; (2) drafting the article and revising it critically for important intellectual content; (3) final approval of the version to be published.

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Figure legend

Fig 1. Study flowchart.

352 type 2 diabetic French subjects and 99 patients from the Israeli HMO were included in the analyses. The test cohort (n=213) consisted of subjects with complete data set at baseline. The French (n=134) and Israeli (n=99) confirmation cohorts was used for Ad-DiaRem external confirmation.

Fig 2 a. Number of glucose-lowering treatments at baseline in the test cohort. Each diagram represents the percentage of patients with the different number of glucose-lowering agents in remission (DR+PDR) and non-remission groups. White bars represent patients not treated with glucose-lowering treatments, light grey bars represent patients treated with one glucose-lowering treatment, dark grey bars represent two glucose-lowering treatments, black bars three glucose-lowering treatments. **b. Evaluation of DiaRem and Ad-DiaRem scores** in French cohorts for DR+PDR vs NDR in the overall test and French confirmation cohorts (DiaRem test (AUC=0.856; Acc=0.789); DiaRem conf (AUC=0.893; Acc=0.881); Ad-DiaRem test (AUC=0.911; Acc=0.841); Ad-DiaRem conf (AUC=0.939; Acc=0.896) **c.** Percent of remission (DR and PDR) according to **DiaRem score** in the test cohort **d.** Distribution of patients according to each **DiaRem score** values in the test cohort. **e.** Distribution of patients according to each **Ad-DiaRem score** values in the test cohort in DR+PDR vs. NDR. **f. Evaluation of DiaRem and Ad-DiaRem scores in subjects with low (0-2) as compared to high scores (19-21 for DiaRem and 19-22 for Ad-DiaRem)** in test cohort and French confirmation cohorts for DR+PDR vs. NDR (DiaRem test (AUC=0.857; Acc=0.873); DiaRem conf (AUC=0.899; Acc=0.846); Ad-DiaRem test (AUC=0.955; Acc=0.944); Ad-DiaRem conf (AUC=0.977; Acc=0.96) **g**. **Evaluation of DiaRem and Ad-DiaRem scores in subjects with low (0-5) as compared to high scores (15-22 for DiaRem and 15-21 for the Ad-DiaRem)** in test cohort and French confirmation cohort for DR+PDR vs. NDR (DiaRem test (AUC=0.857; Acc=0.887); DiaRem conf (AUC=0.891; Acc=0.91); Ad-DiaRem test (AUC=0.935; Acc=0.965); Ad-DiaRem conf (AUC=0.964; Acc=0.96)) **h. DiaRem and Advanced DiaRem scores in subjects with medium score (8-14)** in test cohort and confirmation cohort for DR+PDR vs. NDR. **i.** Distribution of patients according to each **Ad-DiaRem score** values in the confirmation french cohort in DR+PDR vs. NDR **j. DiaRem score in the Israeli** confirmation cohort for DR+PDR vs. NDR. **k.** Ad-DiaRem score in the Israeli confirmation cohort for DR+PDR vs. NDR. **l.**

Evaluation of Ad-DiaRem in all subjects in Israeli confirmation cohorts for DR+PDR vs NDR. (AUC=0.88).

Red bars represent NDR patients and green bars represent DR+PDR patients. Red graphs represent 80% of patients with NDR and Green graphs represent 80% of patients with DR (d, e, I, j, k). Red and blue lines respectively represent the test and confirmation cohorts. Dotted lines and full lines represent respectively DiaRem *and Advanced-DiaRem (b, f, g, h).*

Table 1. Baseline characteristics of Type 2 diabetic patients before bariatric surgery according to remission status at 12 months post-surgery (test cohort)

Variable	Remission group DR+PDR (n=137)	Non-remission group NDR (n=76)	*p* value	Adjusted *p* value
Male N (%)	41 (30)	30 (40)	0.16	-
Age (yrs)	46 ± 10	53 ± 9	<0.01	-
BMI (kg/m^2)	48.1±7.4	45.4 ± 7	0.01	0.09
Hypertension N (%)	88 (65)	67 (89)	<0.01	-
Treated for hypertension N (%)	83 (61)	66 (87)	<0.01	-
Obstructive Sleep Apnea N (%)	101 (75)	61 (81)	0.28	-
Treated with CPAP	58 (43)	37 (50)	0.35	-
Diabetes characteristics				
Diabetes duration (yrs)	3.5 ± 3.8**	11.1 ± 7.6	<0.01	<0.01
Insuline therapy N(%)	13 (9)	42 (55)	<0.01	-
Sulfonylureas or ISA other than metformin N (%)	29 (21)	29 (38)	<0.01	-
Fasting glycaemia (mmol/l)	7.43 ± 2.32**	9.07 ± 0.3.04	0.01	<0.01
Fasting Insulin (pmol/l)	170.14 ± 125	143.75 ± 117.71	0.26	0.89
HbA_{1c} (%)	7.0 ± 1.1**	8.4 ± 1.6	<0.01	<0.01
HbA_{1c} (mmol/mol)	53 ± 11.9	68 ± 17.8		
HOMA-IR	3.3 ± 2.3	2.9 ± 2.2	0.35	0.98
HOMA-B%	115.1 ± 61.7*	78.4 ± 53.1	<0.01	0.03
HOMA-S%	46.5 ± 41.8	54 ± 33.7	0.28	0.49
Body composition				
Fat mass (%)	47.9 ± 5.3**	45.3 ± 5.9	<0.01	<0.01
Fat-free mass (%)	49.9 ± 5.1**	52.4 ± 5.7	<0.01	<0.01
Fat mass/fat-free mass ratio	0.98 ± 0.20**	0.88 ± 0.20	<0.01	<0.01
Android fat mass (%)	66.2 ± 5.5	68.5 ± 5.3	<0.01	0.08
Gynoid fat mass (%)	32.2 ± 5.6*	29.5 ± 5.3	<0.01	0.02
Android/gynoid fat mass ratio	2.15 ± 0.53*	2.42 ± 0.61	<0.01	0.01
Adipokines				
Adiponectin (µg/ml)	4.9 ± 3.2	4.8 ± 2.9	0.97	0.35
Leptin (ng/ml)	52.0 ± 25.9	48.0 ± 32.6	0.37	0.21
Lipid variables				
Treated with lipid-lowering drugs N (%)	48 (35)	55 (72)	<0.01	-
Total cholesterol (mmol/l)	4.88 ± 1.03*	4.39 ± 1.04	<0.01	0.01
Triacylglycerol (mmol/l)	1.90 ± 1.76	1.91 ± 1.13	0.98	0.64
HDL-cholesterol (mmol/l)	1.11 ± 0.32	1.18 ± 0.36	0.16	0.89
Apo-A1 (mmol/l)	1.36 ± 0.25	1.42 ± 0.29	0.19	0.81
Apo-B (mmol/l)	0.99 ± 0.31	0.89 ± 0.26	0.02	0.09
Liver biology				

AST (µkat/L)	0.55 ± 0.30	0.53 ± 0.25	0.63	0.81
ALT (µkat/L)	0.78 ± 0.82	0.67 ± 0.40	0.19	0.93
γGT (µkat/L)	0.91 ± 0.72	1.12 ± 0.88	0.10	0.02
Inflammatory factors				
IL-6 (pg/ml)	4.2 ± 2.1	4.9 ± 3.5	0.14	0.08
hsCRP (mg/l)	10.8 ± 8.9	8.2 ± 9.5	0.06	0.60
Orosomucoid (g/l)	0.94 ± 0.22	0.90 ± 0.23	0.15	0.64
Adipose tissue needle aspirate				
Adipocyte diameter (µm)	121.1 ± 13.9	119.9 ± 9.8	0.53	0.46
Morphology (pl)	46.7 ± 225.4	47.5 ± 216.1	0.98	0.57

Baseline characteristics were compared using Student's t-test for two groups, according to subjects' one-year remission outcomes (i.e. DR+PDR as remission group, NDR as non-remission group) in previously type 2 diabetic subjects. type 2 diabetes was defined according to ADA guidelines (i.e. fasting plasma glucose (FPG) ≥ 7.0mmol/l, 2 hour PG ≥ 11.1mmol/L when available, $HbA_{1c} \geq 6.5\%$, or patients receiving any glucose-lowering agents). Partial diabetes remission (PDR) was defined as $HbA_{1c} < 6.5\%$, FPG < 7.0mmol/l, and no use of glucose-lowering agents at T12; complete diabetes remission (DR) was defined as $HbA_{1c} < 6.0\%$, FPG < 5.6mmol/L and no use of glucose-lowering agents at T12. Continuous data were also adjusted for age. ISA, insulin sensitizing agent. *Denotes statistical significance between Remission and non-Remission groups, *p<0.05, **p<0.01

Table 2 Advanced DiaRem

Prediction factor	Score
Age (yr)	
[15-41]	0
[42-52]	3
[52-69]	5
HbA_{1c} (%)	
[4.5-6.9]	0
[7-7.4]	2
[7.5-18.4]	4
Insulin	
No	0
Yes	3
Other glucose-lowering agents	
No	0
Yes	1
Number of glucose-lowering agents	
0	0
1	1
2	2
≥3	3
Diabetes duration	
[0-6.9],	0
[7-13.9]	3
≥14	5
Ad-Score: sum of the above six components	0-21

For “other glucose-lowering agents”, sulfonylureas include glimepiride, glipizide and glibenclamide; insulin sensitizing agents (ISA) other than metformin include pioglitazone and rosiglitazone. *Number of glucose-lowering agents* takes into account sulfonylureas, ISA and glucagon-like peptide 1 (GLP-1) analogs, dipeptidyl peptidase-4 (DDP-IV) inhibitors, insulin, and other glucose-lowering agents. Ad-Score = advanced score

Figure 1

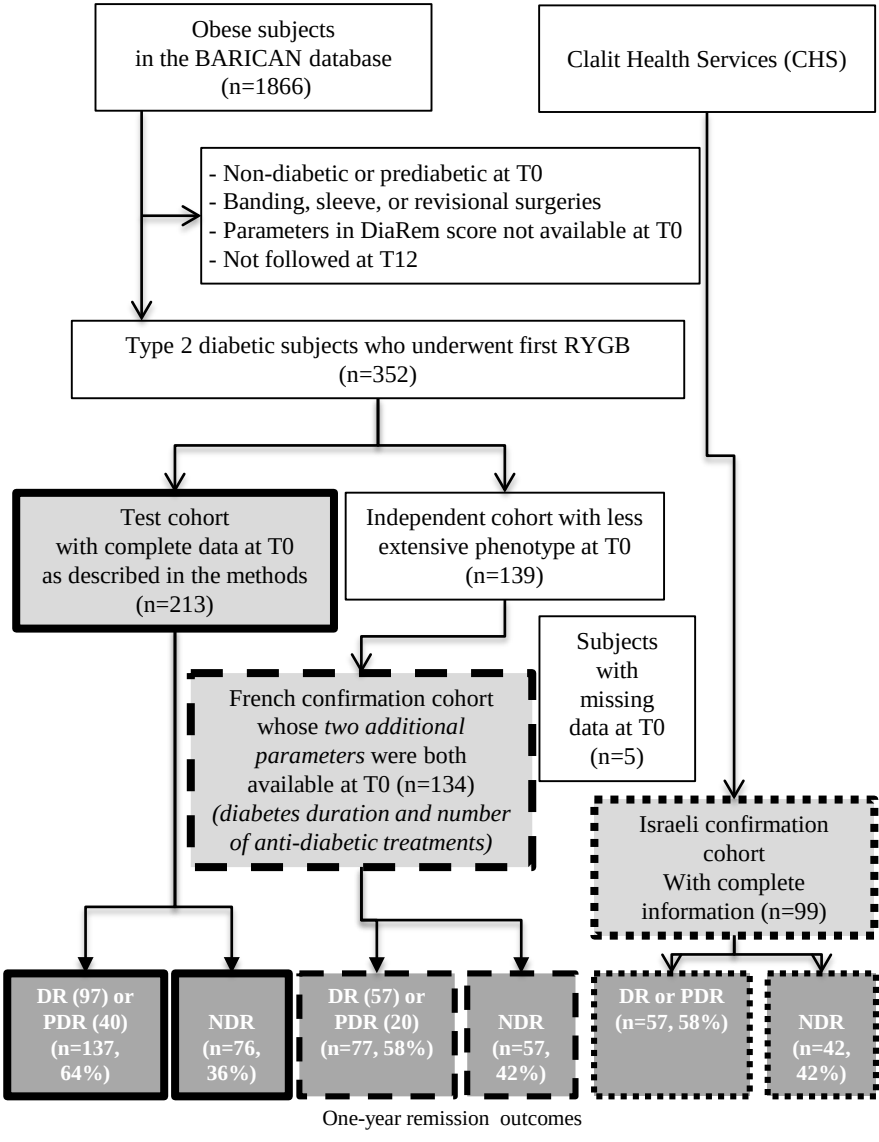
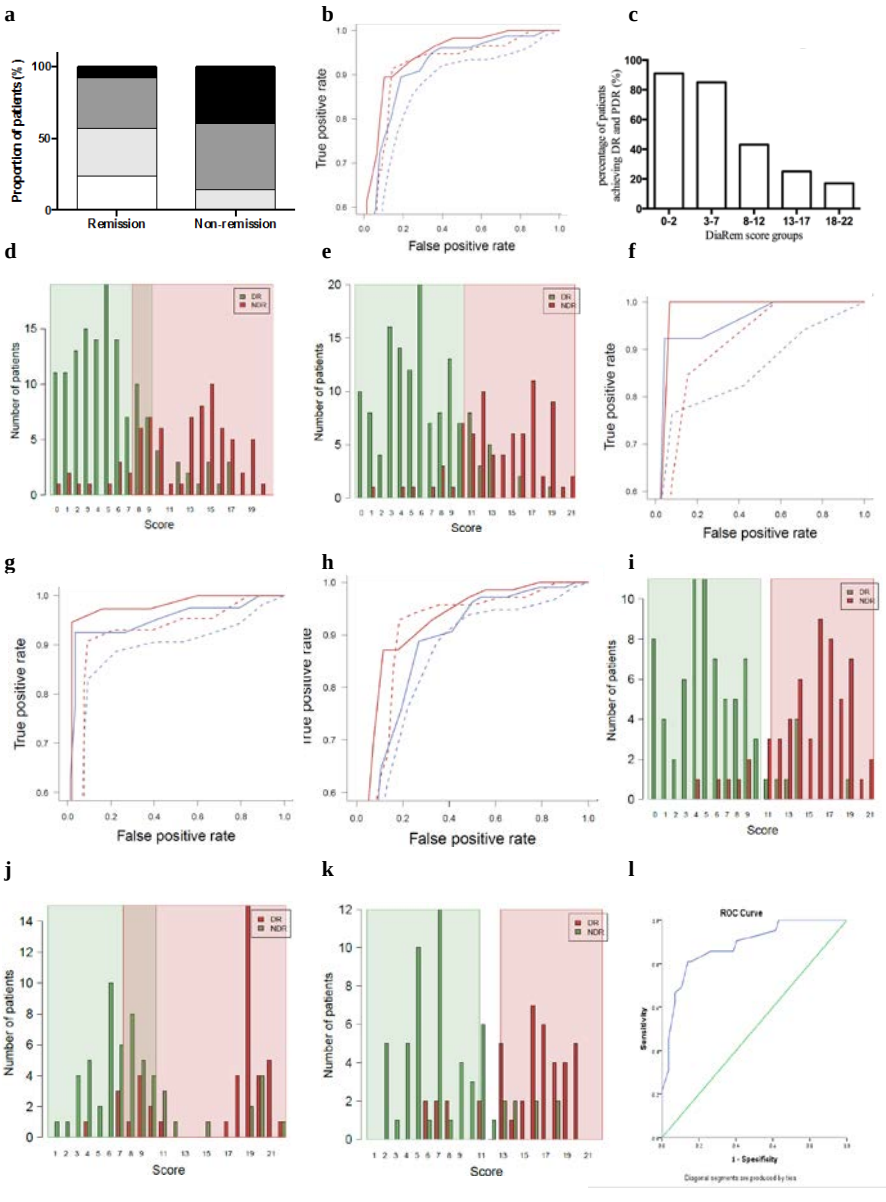

Obese subjects
in the BARICAN database
(n=1866)
Clalit Health Services (CHS)
- Non-diabetic or prediabetic at T0
- Banding, sleeve, or revisional surgeries
- Parameters in DiaRem score not available at T0
- Not followed at T12
Type 2 diabetic subjects who underwent first RYGB
(n=352)
Test cohort
with complete data at T0
as described in the methods
(n=213)
Independent cohort with less
extensive phenotype at T0
(n=139)
Subjects
with
missing
data at T0
(n=5)
French confirmation cohort
whose *two additional parameters* were both
available at T0 (n=134)
(diabetes duration and number of anti-diabetic treatments)
Israeli confirmation
cohort
With complete
information (n=99)
DR (97) or
PDR (40)
(n=137,
64%)
NDR
(n=76,
36%)
DR (57) or
PDR (20)
(n=77, 58%)
NDR
(n=57,
42%)
DR or PDR
(n=57, 58%)
NDR
(n=42,
42%)
One-year remission outcomes

Fig 2


a
Proportion of patients (%)
100
50
0
Remission
Non-remission
b
True positive rate
False positive rate
c
percentage of patients achieving DR and PDR (%)
DiaRem score groups
0-2
3-7
8-12
13-17
18-22
d
Number of patients
Score
DR
NDR
e
Number of patients
Score
DR
NDR
f
True positive rate
False positive rate
g
True positive rate
False positive rate
h
True positive rate
False positive rate
i
Number of patients
Score
DR
NDR
j
Number of patients
Score
DR
NDR
k
Number of patients
Score
DR
NDR
l
ROC Curve
Sensitivity
1 - Specificity